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Changes in the Treatment and Prevention of Heart Failure Based on the 2023 Focused Update of the 2021 European Society of Cardiology Guidelines

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Abstract:

Introduction and Objective:

The 2023 update to the 2021 ESC Guidelines for diagnosing and treating acute and chronic heart failure introduces significant changes in pharmacotherapy and prevention. Staying informed about these updates is crucial given the evolving landscape of heart failure

management. This review provides an overview of the latest recommendations and supporting evidence.

Review Methods:

A comprehensive review of scientific publications and guidelines from PubMed, Google Scholar, Clinical Key, Via Medica Journals, and relevant clinical guidelines was conducted to ensure the most recent evidence is considered.

Brief Description of the State of Knowledge:

Heart failure is a growing global concern. The 2023 update highlights key management changes. Recent trials, including EMPEROR-Preserved and DELIVER, show empagliflozin and dapagliflozin reduce heart failure hospitalization and cardiovascular death in patients with mildly reduced and preserved ejection fraction. The guidelines now recommend intravenous iron for patients with reduced or mildly reduced ejection fraction and iron deficiency. For those with type 2 diabetes and chronic kidney disease, SGLT2 inhibitors and finerenone, a non-steroidal mineralocorticoid antagonist, are recommended to reduce heart failure hospitalization and prevent renal function decline.

Summary:

The 2023 ESC Guidelines update offers revised recommendations for heart failure management and prevention, integrating the latest clinical trial data and meta-analyses. Key areas include the use of SGLT2 inhibitors, iron deficiency management, and preventive strategies for high-risk populations. Implementing these guidelines can significantly improve preventive and therapeutic outcomes for heart failure patients.

Keywords: Heart Failure; Cardiovascular Diseases; Heart Diseases; Iron Deficiencies; Kidney Diseases

Introduction

Heart failure (HF) is a clinical syndrome resulting from structural or functional abnormalities of the heart.[1] This condition is caused by a disorder of filling or ejection of blood from the heart's ventricle(s), which results in reduced cardiac output or increased intracardiac pressure at rest or during stress.[2] These phenomena lead to a range of symptoms such as: fatigue,

dyspnoea, exercise intolerance, and despite often accompanying abnormal findings in physical examination (e.g. ankle oedema, increased jugular venous pressure, hepatojugular reflux, pulmonary crackles), it is the clinical symptoms that are essential for diagnosing heart failure.[3,4] The most common cause of HF is myocardial dysfunction – in developed countries primarily resulting from ischemic heart disease in the course of coronary artery disease. However, pathology can also involve the valves, pericardium, endocardium, or the cardiac conduction system, and thus identifying the source of the abnormality is crucial in selecting the appropriate treatment.[5,6] Despite significant advances in both HF prevention and modern treatment methods, morbidity and mortality remain high. In developed countries, this condition affects approximately 1-2% of the adult population, utilizing substantial healthcare resources and generating significant costs.[7,8] Only about 50% of patients survive five years post-diagnosis, with a median survival time from the onset of clinical symptoms being six years.

In addressing the challenge that HF presents to healthcare, scientific societies support clinicians by publishing guidelines based on current research to help decision-making in the therapeutic process for HF patients.

ESC Guidelines and Focused Updates

One such society is the European Society of Cardiology (ESC), a non-profit professional association comprising 57 National Cardiac Societies and 28 subspecialty communities. One aspect of ESC's extensive activities aimed at reducing the burden of cardiovascular diseases is the publication of guidelines containing up-to-date, evidence-based knowledge on the prevention, diagnosis, and management of cardiovascular diseases. These guidelines are developed in accordance with strict rules and procedures, regularly updated, and made available for free. In addition to the full guidelines published periodically every few years, there are situations where ESC decides to issue a focused update with new and improved guidelines in light of new, strong data. This occurs when delaying guideline updates would harm patients, as implementing newly proposed treatment strategies based on new evidence can bring tangible benefits. Such a situation occurred on October 1, 2023, with the release of the 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. New data emerged in areas such as the treatment of patients with heart failure with mildly reduced and preserved ejection fraction, management of iron

deficiency in HF patients, and prevention of HF in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM). These changes are discussed below.

Heart Failure with Preserved Ejection Fraction (HFpEF) and HF with Mildly Reduced Ejection Fraction (HFmrEF)

A commonly used classification in clinical practice of heart failure is the one based on left ventricular ejection fraction (LVEF) – the fraction of chamber volume ejected in systole in relation to the volume of blood in the ventricle at the end of diastole. Depending on this, HF is divided into heart failure with preserved ejection fraction (LVEF ≥ 50%), heart failure with mild range ejection fraction (LVEF 40-49%), and heart failure with reduced ejection fraction (LVEF < 40%). [9] The 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure contained strong recommendations for the use of disease-modifying therapies for HF with reduced ejection fraction (HFrEF), but the trials on which they were based were not designed for those with HF with mildly reduced or preserved ejection fraction. As a result, the 2021 guidelines provided only weak recommendations for patients with HFmrEF, and there were no recommendations for patients with HFpEF in this regard.

Pharmacotherapy in the treatment of HF aims to prolong life, prevent hospitalizations caused by exacerbations, and alleviate symptoms. [10] In the case of HFrEF, treatment based on four groups of drugs has proven effective in these aspects.[11] The first group consists of modulators of the renin-angiotensin-aldosterone system (RAAS) – angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI). They offer many benefits in HF, such as reducing preload and afterload, increasing cardiac output, and slowing left ventricular remodeling. [12] Drugs added in therapy to ACE-I/ARNI are beta-blockers, which, thanks to their antiarrhythmic, anti-ischemic properties, and by reducing blood pressure and heart rate, improve ventricular function in HF. [13] Alongside these, mineralocorticoid receptor antagonists (MRA), such as spironolactone or eplerenone, hold a strong position. MRAs inhibit myocardial fibrosis, thus improving systolic and diastolic function of the left ventricle and also have hypotensive effects.[14] The last group of drugs that found a place in basic HFrEF therapy is relatively new – sodium-glucose cotransporter-2 inhibitors, like dapagliflozin - the first approved in the European Union in 2012, and empagliflozin, which appeared two years later.[15,16] These two drugs were the subject of large-

scale studies (EMPEROR and DELIVER), which led to ESC deciding to formulate the focused update.[17]

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors, also known as gliflozins) are medications that strongly and selectively inhibit the activity of SGLT-2, a glucose cotransporter found almost exclusively in the epithelial cells of the proximal renal tubules. This results in decreased reabsorption of glucose in the kidneys, increased urinary glucose excretion, and consequently lower blood glucose levels.[18] The hypoglycemic effect of this drug class is therefore independent of insulin (or insulin resistance), improving both fasting and postprandial blood glucose levels. There is no impact on endogenous glucose production, and the amount of glucose lost in urine depends on its blood concentration, making the risk of hypoglycemia during therapy with these drugs minimal.[19] Due to these advantages, SGLT-2 inhibitors quickly joined the ranks of drugs used in the treatment of type 2 diabetes mellitus (T2DM). They are used at every stage of disease management and, while primarily used in combination with other hypoglycemic agents, they can also be used as monotherapy.[20]

In addition to their role in glycemic control, SGLT-2 inhibitors have antihypertensive effects (resulting from osmotic diuresis and increased natriuresis), help in weight reduction (linked to the caloric content of glucose lost in urine), and positively affect the lipid profile.[21] Collectively, these actions contribute to cardiovascular disease prevention by modifying risk factors such as T2DM, excessive body weight, hypertension, and lipid disorders. Furthermore, they improve heart hemodynamics and metabolism and also inhibit myocardial fibrosis, giving them a cardioprotective character.[22]

Evolution of SGLT-2 Inhibitors Recommendations in Heart Failure Therapy

The multifactorial beneficial impact on the cardiovascular system has been proven in multiple randomized clinical trials and meta-analyses. Therefore, it is no surprise that SGLT-2 inhibitors were included in several indications in the 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, specifically in glucose-lowering treatment in patients with T2DM and cardiovascular disease, and in

T2DM treatment to reduce heart failure risk, each receiving class I recommendations and level A evidence. Soon after, evidence emerged showing the benefits of dapagliflozin and empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) regardless of concomitant diabetes mellitus. Accordingly, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure included recommendations for dapagliflozin or empagliflozin for patients with HFrEF to reduce the risk of hospitalization and death (class I recommendations, level A evidence). However, for patients with heart failure with mildly reduced ejection fraction (HFmrEF), only pharmacological treatments to be considered to reduce the risk of HF hospitalization and death were mentioned with a class of recommendation - IIb and level of evidence - C. This recommendation pertained to the use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-receptor blockers (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNI). For patients with heart failure with preserved ejection fraction (HFpEF), there were no recommendations for disease-modifying therapies at that time.[23]

New Scientific Evidence and Recommendations for SGLT-2 Inhibitors

Significant changes occurred with the 2023 Focused Update of the 2021 ESC Guidelines, which incorporated the results of two studies on SGLT-2 inhibitors.

The first study, the EMPEROR-Preserved trial, involved administering 10 mg of empagliflozin once daily to patients with HF and raised plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) with preserved or mildly reduced ejection fraction (LVEF >40%). The study included 5988 patients who were randomly assigned to either the drug group or the placebo group. Most patients were also receiving ACE-I/ARB/ARNI and beta-blockers, with some also taking MRA. The primary outcome was a composite of cardiovascular death or hospitalization for HF. The median follow-up period was 26.2 months, and the primary endpoint was reduced due to a lower rate of HF hospitalizations with empagliflozin. This effect was observed in both T2DM and non-T2DM patients.

The second significant study, the DELIVER trial, was conducted similarly. It involved 6263 patients with HF, raised NT-proBNP concentrations, and LVEF >40%, who were divided into a control group receiving placebo and a study group receiving 10 mg of dapagliflozin once

daily. The primary outcome was a composite of worsening HF (which was defined as either an unplanned hospitalization for HF or an urgent visit for HF) or cardiovascular death, as assesed in a time-to-event analysis. The main benefit of dapagliflozin was in reducing worsening HF, with a non-significant effect on cardiovascular death. Additionally, dapagliflozin was noted to reduce the severity of HF symptoms.

A meta-analysis based on the DELIVER and EMPEROR-Preserved trials confirmed a 26% reduction in HF-caused hospitalizations and demonstrated effects across the entire range of LVEF studied. While no significant reduction in cardiovascular death was observed, another meta-analysis including data from both DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) study in HFrEF and DELIVER indicated that dapagliflozin also reduces the risk of cardiovascular death.

Based on the new evidence, the 2023 Focused Update of the 2021 ESC Guidelines now recommends an SGLT-2 inhibitor (dapagliflozin or empagliflozin) for patients with HF with mildly reduced and preserved ejection fraction to reduce the risk of HF hospitalization or cardiovascular death.[17]

Iron Deficiency in Heart Failure

Improving the prognosis of a patient with heart failure (HF) involves not only treating the primary disease but also addressing comorbidities. One such comorbidity is iron deficiency, which, either accompanied by anemia or not, is a negative prognostic factor in HF patients. It is associated with an increased risk of HF-related hospitalizations, high overall and cardiovascular mortality, and more severe symptoms, resulting in reduced physical capacity and a lower quality of life.[24]

About 30% of HF patients are affected by iron deficiency, which often manifests as chronic normocytic anemia. There are multiple potential causes for this coexistence. HF can contribute to reduced iron absorption from the gastrointestinal tract, not only due to decreased appetite and insufficient iron intake but also because of intestinal edema and enterocyte dysfunction, which disrupts calcium absorption. Another cause may be iron loss; many HF patients require antiplatelet and anticoagulant medications due to cardiovascular comorbidities, which increase the risk of chronic blood loss by affecting coagulation. Additionally, HF can lead to functional iron deficiency – during systemic inflammation,

increased production of inflammatory cytokines impacts iron metabolism, aiming to reduce iron availability to bacteria but simultaneously disrupting iron utilization in hematopoiesis.[24,25]

The ESC guidelines have already strongly recommended regular screening for anemia and iron deficiency in all HF patients by monitoring complete blood count, serum ferritin levels, and transferrin saturation. Oral iron supplementation in HF patients is not an effective way to correct iron deficiencies, as studies have not shown improvements in physical capacity in HFrEF patients with iron deficiency.[26] Erythropoiesis-stimulating agents, such as darbepoetin alfa (a protein structurally similar to erythropoietin with the same mechanism of action), also do not appear to be a good therapeutic option for HF patients, since a large clinical trial in HFrEF patients with mild to moderate anemia indicated an increased risk of thromboembolic events without reducing HF hospitalizations or mortality.[27]

A suitable solution for these patients is intravenous iron supplementation using ferric carboxymaltose, which is safe and beneficial for symptoms, physical capacity, and quality of life in HFrEF patients with iron deficiency. In the 2021 ESC guidelines, intravenous iron supplementation with ferric carboxymaltose received a class IIa recommendation due to insufficient evidence. However, in light of new studies (FAIR-HF, CONFIRM-HF, AFFIRM-AHF, and IRONMAN) and meta-analyses, intravenous iron supplementation is now recommended in patients with HFrEF or HFmrEF and iron deficiency to improve symptoms and quality of life (class I recommendations and level A evidence). In the same patient group, this approach should also be considered for reducing the risk of HF hospitalization, although, despite the level A evidence, the class of recommendation remains IIa.[17]

Prevention of Heart Failure Development in At-Risk Patient Population

The 2023 Focused Update of the 2021 ESC Guidelines once again emphasizes the importance of preventing heart failure. Many currently prevalent chronic diseases, such as hypertension, coronary artery disease, diabetes, and chronic kidney disease, carry a high risk of developing HF.,[28,29] Hence, scientific findings on how to counteract this progression are highly significant. This time, the guidelines include recommendations for patients simultaneously afflicted with type 2 diabetes and chronic kidney disease (CKD). The frequent overlap of these two diseases

is due not only to diabetes being a leading cause of chronic kidney failure but also to common risk factors such as hypertension, poor diet, obesity, and smoking.

The first recommendation once again involves SGLT-2 inhibitors, based on conclusions from two randomized controlled trials (DAPA-CKD and EMPA-KIDNEY) and a resulting meta-analysis.

DAPA-CKD involved 4304 patients with varying degrees of renal impairment (with a urinary albumin-to-creatinine ratio ≥200 mg/g and an eGFR of 25–75 mL/min/1.73 m²). Among the study participants were both individuals with and without diabetes, and 11% had a history of HF. Patients were randomly assigned to receive either 10 mg of dapagliflozin daily or a placebo. The primary endpoint was a sustained decline in eGFR of ≥50%, end-stage kidney disease, or kidney-related or cardiovascular death. Over an average follow-up period of 2.4 years, dapagliflozin showed superiority over placebo, reducing the primary endpoint by 39%.

EMPA-KIDNEY involved 6609 patients with a broader spectrum – those with an eGFR of 45–90 mL/min/1.73 m² and a urinary albumin-to-creatinine ratio ≥200 mg/g, as well as patients with an eGFR of 20–45 mL/min/1.73 m² regardless of albuminuria. About 10% had a history of HF. The primary composite endpoint was the progression of kidney disease or cardiovascular death, which was also reduced after a median follow-up of 2.0 years.

These two studies, combined with other relevant research – CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) and SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) – were used for a meta-analysis. Based on these findings, the recommendation to use SGLT-2 inhibitors in patients with CKD and T2DM to reduce the risk of HF hospitalization or cardiovascular death was formulated (currently for patients with an eGFR >20–25 mL/min/1.73 m² due to the profile of study participants).[17]

Sodium–glucose co-transporter 2 inhibitors are not the only drugs highlighted in the 2023 Focused Update of the 2021 ESC Guidelines for patients with type 2 diabetes and CKD. Evidence of benefits in this patient group also pertains to finerenone – a new-generation non-steroidal mineralocorticoid receptor antagonist (MRA). Traditional steroidal MRAs pose risks such as hyperkalemia and renal function deterioration, and spironolactone, in particular,

carries a risk of gynecomastia and menstrual disturbances due to its affinity for androgen and progesterone receptors. These side effects limit their use, making finerenone a promising alternative.

Studies have shown that finerenone has high selectivity for the mineralocorticoid receptor, with over 500 times the affinity in comparison to the glucocorticoid, androgen, and progesterone receptors, providing an advantage over spironolactone. Compared to eplerenone, finerenone's higher affinity for the mineralocorticoid receptor means that lower doses of finerenone achieve similar clinical effects as higher doses of spironolactone or eplerenone. Another advantage of finerenone for HF patients is its distribution profile; unlike steroidal MRAs, which are more distributed to kidney cells than heart cells, finerenone reaches both organs equally, exerting beneficial effects on the heart at relatively low doses while posing a lower risk of renal side effects, such as hyperkalemia and reduced eGFR.[30]

Finerenone's place in the 2023 Focused Update of the 2021 ESC Guidelines results from two studies involving patients with diabetic kidney disease – the FIDELIO-DKD and FIGARO-DKD trials.

In the FIDELIO-DKD trial, the primary outcome was a composite of kidney failure, a sustained decrease of ≥40% in the eGFR from baseline over a period of ≥4 weeks, or death from renal causes. Kidney failure was defined as a reduction in eGFR to <15 mL/min/1.73 m², the need for dialysis for ≥90 days, or kidney transplantation. This study included 5734 patients, and over a median follow-up of 2.6 years, the primary endpoint was reduced by 18% with finerenone compared to placebo. However, FIDELIO-DKD did not provide evidence of reduced HF hospitalization frequency with finerenone.

Such evidence emerged later in the FIGARO-DKD trial, where the primary outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or HF hospitalization. Conducted on 7437 participants with a median follow-up of 3.4 years, the trial concluded that finerenone treatment was superior to placebo in the studied patient group, mainly by reducing HF hospitalization rates without significant differences in cardiovascular mortality.

Both the FIDELIO-DKD and FIGARO-DKD trials, along with the subsequent analysis, provided reasons for recommending finerenone for preventing HF hospitalizations in patients with chronic kidney disease and T2DM.[17]

Conclusion

The development of heart failure impairs the quality of life and can even shorten its duration. Despite significant advances in knowledge about it, heart failure remains a serious problem. Clinical guidelines published by scientific societies, such as the European Society of Cardiology (ESC), are a great help to clinicians. These guidelines are based on the latest scientific research, which helps ensure the best possible medical care for patients. The goals of heart failure treatment are to alleviate symptoms, prevent hospitalizations, and prolong life. In the pharmacotherapy of heart failure, groups of drugs such as renin-angiotensin-aldosterone system modulators (ACE-I, ARNI), beta-blockers, mineralocorticoid receptor antagonists (spironolactone, eplerenone), and sodium-glucose cotransporter-2 inhibitors (dapagliflozin, empagliflozin) are used.

SGLT-2 inhibitors contribute to the prevention of cardiovascular diseases by lowering blood glucose levels, exerting a hypotensive effect, aiding in weight reduction, and having a favourable impact on lipid profiles. They also have cardioprotective effects by inhibiting myocardial fibrosis. The results of the EMPEROR-Preserved trial, which utilized empagliflozin, and the DELIVER trial, which used dapagliflozin, have led to changes in the guidelines for treating individuals with heart failure. In the 2023 Focused Update of the 2021 ESC Guidelines, SGLT2 inhibitors are recommended to reduce the risk of hospitalization due to heart failure or cardiovascular death not only in individuals with an ejection fraction ≤40% but also in those whose ejection fraction is mildly reduced or preserved (class I recommendations and level A evidence).

Another issue addressed in the 2023 Focused Update of the 2021 ESC Guidelines is iron deficiency. Approximately 30% of people with heart failure are affected by it. Iron deficiency is associated with more severe HF symptoms, an increased risk of hospitalization due to HF, and high overall and cardiovascular mortality. Causes of this condition include, among others: decreased appetite, reduced absorption, chronic blood loss, and a generalized inflammatory state. The results of new studies and meta-analyses have led to the formulation of two

recommendations regarding intravenous iron supplementation in individuals with heart failure. I.v. iron supplementation is now recommended in patients with HFrEF or HFmrEF and iron deficiency to improve symptoms and quality of life (class I recommendations and level A evidence). In the same group of patients, this approach should also be considered to reduce the risk of HF hospitalization (class IIa recommendations and level A evidence).

The new guidelines also address the prevention of heart failure in individuals concurrently burdened with chronic kidney disease (CKD) and type 2 diabetes (T2DM). A recommendation has been formulated for the use of SGLT2 inhibitors in patients with CKD and T2DM to reduce the risk of HF hospitalization or cardiovascular death in patients meeting the criterion of eGFR >20–25 mL/min/1.73 m^2 based on the profile of study participants (class I recommendations and level A evidence). In addition to SGLT2 inhibitors, the use of finerenone is also recommended in this group of patients (with CKD and T2DM) for the prevention of HF hospitalization (class I recommendations and level A evidence). Finerenone is a drug from the group of mineralocorticoid receptor antagonists (MRAs). It has higher selectivity for the mineralocorticoid receptor than spironolactone and greater affinity for this receptor than eplerenone. As a result, the same clinical effect is achieved at lower doses compared to the classical drugs in this group. Finerenone distributes equally to the cells of the heart and kidneys (whereas steroidal MRAs primarily distribute to the kidneys), allowing for a beneficial effect on the heart at relatively low doses, and the risk of side effects such as hyperkalemia or a decrease in eGFR remains relatively low.

The ESC guidelines present a comprehensive approach not only to heart failure but also to other cardiovascular diseases. They cover topics such as prevention, diagnosis, and treatment. The guidelines are regularly updated and made available for free, providing invaluable assistance to physicians in making clinical decisions.

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